AD-A102 497 OKLAHOMA UNIV HEALTH SCIENCES CENTER OKLAHOMA CITY   F/6 6/15
EFFECTIVENESS OF STEROID/ANTIBIOTIC TREATMENT IN PRIMATES ADMIN--ETC(U)
JUL 81 L B HINSHAW, B K BELLER-TODD   N00014-79-C-0854
UNCLASSIFIED TR-144   NL

END
DATE
FILMED
8-81
DTIC

EFFECTIVENESS OF STEROID/ANTIBIOTIC TREATMENT

IN PRIMATES ADMINISTERED LD_{100} ESCHERICHIA COLI

Lerner B. Hinshaw, Beverly K. Beller-Todd, Linda T. Archer,

Bruce Benjamin, Dayl J. Flournoy, Richard Passey, Michael F. Wilson

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER Technical Report No. 144	2. GOVT ACCESSION NO. AD-AZOZ 497	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) EFFECTIVENESS OF STEROID/ANTIBIOTIC TREATMENT IN PRIMATES ADMINISTERED LD100 ESCHERICHIA COLI		5. TYPE OF REPORT & PERIOD COVERED Technical Report 6. PERFORMING ORG. REPORT NUMBER 144
7. AUTHOR(s) Lerner B. Hinshaw, Beverly K. Beller-Todd, Linda T. Archer, Bruce Benjamin, Dayl J. Flournoy, Richard Passey, and Michael F. Wilson		8. CONTRACT OR GRANT NUMBER(s) N00014-79-C-0854
9. PERFORMING ORGANIZATION NAME AND ADDRESS University of Oklahoma Health Sciences Center P.O. Box 26901, Oklahoma City, OK 73190		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS NR 207-207
11. CONTROLLING OFFICE NAME AND ADDRESS Office of Naval Research Arlington, Virginia		12. REPORT DATE July 1981 13. NUMBER OF PAGES
14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office) TR-144		15. SECURITY CLASS. (of this report)
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Distribution of this report is unlimited

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)
Septic shock, steroid therapy, antibiotic therapy, combined steroid/antibiotic treatment, nonhuman primates, baboons, E. coli-induced shock, methylprednisolone sodium succinate, gentamicin sulfate, and endotoxin shock

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)
Early aggressive therapy with maintenance infusions of methylprednisolone sodium succinate and gentamicin sulfate significantly increases the probability for survival of baboons given LD_{100} E. coli. The present study was designed to determine if baboons would recover when initiation of treatment was delayed until they had sustained E. coli-induced systemic hypotension for a period of approximately three hours. Sixteen adult baboons were each administered a two-hour infusion of LD_{100} E. coli.

All eight untreated animals died within 42 hours. Five of the eight baboons treated after approximately three hours of hypotension with methylprednisolone sodium succinate and gentamicin sulfate permanently survived. Treated animals had significantly higher blood glucose and insulin levels and lower blood urea nitrogen concentrations than baboons receiving E. coli alone. E. coli blood concentrations were lower in the treated than in the untreated baboon group by the sixth hour (<0.02). Heart rates increased in all animals but were not as high in the treated baboons. Both groups experienced similar decreases in mean systemic arterial pressure, pCO_2, base excess, leukocyte, lymphocyte, and platelet concentrations, and increases in creatinine and lactate concentrations. Data from the present study indicate that the probability of recovery from shock is significantly increased even when initiation of steroid/antibiotic therapy is postponed until baboons have experienced sustained systemic hypotension.

ABSTRACT

Early aggressive therapy with maintenance infusions of methylpred-
nisolone sodium succinate and gentamicin sulfate significantly increases
the probability for survival of baboons given LD_{100} E. coli. The
present study was designed to determine if baboons would recover when
initiation of treatment was delayed until they had sustained E. coli-
induced systemic hypotension for a period of approximately three hours.
Sixteen adult baboons were each administered a two-hour infusion of
$LD_{\overline{100}}$ E. coli. All eight untreated animals died within 42 hours. Five
of the eight baboons treated after approximately three hours of hypo-
tension with methylprednisolone sodium succinate and gentamicin sulfate
permanently survived. Treated animals had significantly higher blood
glucose and insulin levels and lower blood urea nitrogen concentrations
than baboons receiving E. coli alone. E. coli blood concentrations were
lower in the treated than in the untreated baboon group by the sixth
hour (< 0.02). Heart rates increased in all animals but were not as high
in the treated baboons. Both groups experienced similar decreases in
mean systemic arterial pressure, pCO_2, base excess, leukocyte, lymphocyte,
and platelet concentrations, and increases in creatinine and lactate
concentrations. Data from the present study indicate that the probability
of recovery from shock is significatly increased even when initiation
of steroid/antibiotic therapy is postponed until baboons have experienced
sustained systemic hypotension.

Key Words:

Septic shock, steroid therapy, antibiotic therapy, combined steroid/antibiotic
treatment, nonhuman primates, baboons, E. coli-induced shock, methylprednisolone
sodium succinate, gentamicin sulfate, endotoxin shock.

INTRODUCTION

In an attempt to find a clinically relevant therapy for sepsis and/or septic shock, we have developed a regimen to treat E. coli-shocked baboons consisting of combined multiple infusions of methylprednisolone sodium succinate (MPSS) and gentamicin sulfate (GS) (1, 2). When MPSS treatment is initiated 30 minutes after the onset of a two-hour infusion of LD_{100} E. coli and GS infusion begun after termination of the E. coli infusion all baboons survive (1). GS infusion alone, on the other hand, failed to prevent death (1). Delaying initiation of MPSS infusion until all E. coli are infused results in an 85% survival rate (2). Results from these and parallel studies also demonstrated that administration of either agent alone showed no improvement or reversal of physiopathologic parameters, and the mortality rate remained unchanged (1-4).

The physician is often faced with septic patients who have succumbed to severe systemic hypotension. Consequently, we designed the present study to modify our nonhuman primate septic shock model to more closely resemble that clinical situation by delaying initiation of steroid and antibiotic treatment until severe sustained systemic hypotension had occurred. We chose the baboon to study because of its phylogenetic proximity to man and because of our recent successful work using it as an experimental septic shock model.

Findings clearly support the effectiveness of the steroid/antibiotic combination treatment and indicate that its life-saving characteristics are enhanced by early administration.

MATERIALS AND METHODS

Sixteen adult baboons of the subspecies, Papio c. cynocephalus, were allowed to stabilize 1 to 2 months in the animal facility, fasted

24 hours and given water ad libitum prior to experimentation. The
morning of the study they were immobilized with ketamine hydrochloride,
14 mg/kg, intramuscularly, and intravenously anesthetized with sodium
pentobarbital via a percutaneous catheter positioned in the cephalic
vein. The radial and cephalic vein were exposed aseptically and
cannulated to measure pressures, sample blood and infuse live organisms,
isotonic sodium chloride, methylprednisolone sodium succinate (MPSS) and
gentamicin sulfate (GS). Each baboon was placed on its side between
controlled-temperature heating pads, and a temperature probe was placed
in the rectum. A tracheal cannula was orally inserted, and periodic
positive pressure was applied hourly to prevent atelectasis. Each
animal was allowed to equilibrate at least one hour before beginning
E. coli infusion.

Baboons of either sex were divided into two groups and each infused
with live E. coli for two hours: the control group (N=8; average weight,
16.8 kg) were given 2.4 ($\pm$0.2)x10^{10} organisms/kg body weight prepared as
previously described (1, 3, 4). The experimental group (N=8; average
weight, 17.9 kg) received 2.5 ($\pm$0.2)x10^{10} E. coli/kg body weight, the
steroid, methylprednisolone sodium succinate (MPSS; The Upjohn Company,
Kalamazoo, MI), and the antibiotic, gentamicin sulfate (GS; Schering
Pharmaceutical Corporation, Kenilworth, NJ), as shown in Table 1.

MPSS and GS infusions were begun 2 hours after live organism
administration was complete, that is, 4 hours after initiation of E. coli
infusion. Baboons in the experimental group were administered a total
of 18 mg/kg GS and 75 mg/kg MPSS from the fourth to the twelfth hour.
Normal saline was infused in each baboon of both groups, 6-7 ml/kg/hr,
during the 12-hour period to prevent dehydration, and control animals

received additional saline as a substitute for the drug volumes. Treated baboons were additionally injected intramuscularly with GS at 12 hours and twice daily for 3 days. Baboons were maintained in the animal facility and observed a minimum of 7 days, then arbitrarily euthanized between 7 and 15 days.

Blood pressure and heart rate were monitored with a Sanborn recorder. Arterial blood samples were taken for determinations of glucose, insulin, lactate, white blood cells and differential leukocyte concentrations, platelets, pH, pCO_2, pO_2, blood urea nitrogen, creatinine, serum gentamicin, and blood concentrations of viable E. coli, as previously reported (1-3).

Data were analyzed using the Student's t test for paired and unpaired data and the Fisher's Exact Test for survival statistics.

RESULTS

Untreated baboons and baboons administered MPSS and GS following sustained systemic hypotension induced by E. coli infusion were continuously monitored for 12 hours, then observed up to 15 days. A minium of seven days was required for a baboon to be called a "permanent survivor". Table II records survival times and show that all baboons given E. coli alone, died within 42 hours (mean, 17 hours). Five of the eight baboons treated with MPSS/GS permanently survived. Using Fisher's Exact Test, the survival results are statistically significant for the treated compared with the untreated group (p < 0.05). During recovery, 4 of 5 permanent survivors developed dermal ulcerations of the pelvic, hind limb, or gluteal areas which were treated with septisol, hydrogen peroxide and Panolog®ointment (Squibb).

Table III enumerates the E. coli blood concentrations of the two groups. Each baboon's blood culture was negative at zero time. Five minutes after E. coli infusion was completed (+125 min) blood concentrations

were similar in both groups, approximately 10^7 E. coli per ml blood. By
six hours after the onset of organism infusion, the concentration of
E. coli in the treated group was significantly lower than that of the
control group (p < 0.02).

Figure 1 illustrates the changes in mean systemic arterial pressures
(MSAP) and heart rates (HR) for both groups. The MSAP means of the treated
baboons were lower compared with the zero time value at 1 through 6 hours
(p < 0.05) and the MSAP means of the untreated group were significantly
less than their zero time value from 2 through 4 hours. However, the
MSAP of the two groups did not differ significantly from each other
during the 12-hour observation period. Consequently, each baboon
experienced marked sustained systemic hypotension (approximately 2-3 hours)
before treatment was initiated at 4 hours. Mean heart rates of both groups
were significantly higher than zero time values from 1 through 12 hours,
but heart rates of the treated baboons were less than those of the
untreated animals from 3 through 12 hours (p < 0.05).

Figure 2 pictures changes in blood glucose and serum insulin concen-
trations of treated and untreated baboons. All baboons became hypoglycemic
and hypoinsulinemic by 4 hours. Blood glucose and serum insulin levels
in treated animals returned to normal levels by 12 hours, while those of
the untreated baboons remained low.

Total leukocyte concentrations were significantly decreased from
zero time levels in both groups at 2 and 4 hours after initiation of
E. coli infusion; however, leukocyte concentrations of treated animals were
returning toward normal at 8 and 12 hours. Decreased concentrations of
mature and immature neutrophils appear to be recovering in the treated
baboons from 8-12 hours (Figure 3). Lymphocyte concentrations decreased
similarly in both groups of animals. Platelet concentrations decreased

progressively throughout the 12 hours of monitoring ($p < 0.05$) in both groups with no statistical differences between treated and untreated baboons (Figure 3).

Figure 4 shows pH, pCO_2, HCO_3^-, base excess, and lactate concentrations for the treated and untreated baboons. PCO_2, HCO_3^-, and base excess decreased and lactate increased in both groups from 4 through 12 hours ($p < 0.05$). Both groups maintained relatively constant pH and pO_2 levels during the monitoring period. No statistically significant differences between the two groups were found in any of these parameters during 12 hours.

Blood urea nitrogen (BUN) concentrations moderately increased in both groups (Figure 5), but the values of the treated group were lower at 8 and 12 hours than those of the untreated group ($p < 0.05$). Creatinine concentrations increased similarly in all baboons. Mean serum gentamicin sulfate concentrations in the eight treated animals were 27.7 (±3.3), 20.4 (±2.6), and 26.6 (±4.8) ug/ml at 5.5, 10.5 and 12 hours, respectively. Urine flow was observed in the treated baboons, but the untreated animals were anuric.

Saline administration was similar in both groups with an average of 6 and 7 ml/kg/hr infused in untreated and treated baboons, respectively. Hematocrits of the two groups did not significantly differ; values ranged from 43 to 47% in untreated baboons and from 45 to 50% in treated animals.

DISCUSSION

We recently reported that combined glucocorticoid and antibiotic therapy effectively reverses or prevents the lethal pathophysiology of E. coli-induced shock in both dogs (5) and nonhuman primates (1, 2). We documented that baboons administered LD_{100} E. coli are effectively treated with infusions of methylprednisolone sodium succinate (MPSS)

administered after one-fourth of the organisms are given, followed by subsequent infusions of MPSS and gentamicin sulfacte (GS) during a 12-hour period [1]. All animals treated thusly were healthy permanent survivors. Although a massive number of organisms had been administered (7×10^9 organisms/kg body weight) prior to MPSS treatment in that study [1], aortic pressure had not yet fallen to the lowest point it would have had treatment not been initiated. A second study [2] was designed to extend this work by delaying steroid/antibiotic treatment until all organisms were given (2.5×10^{10} organisms/kg body weight) to allow the early maximal drop in blood pressure to occur prior to beginning steroid treatment [2]. Although 85% of the baboons thus treated were permanent survivors, they returned to normal eating and physical activities slowly and some developed body surface ulcers.

The present study was designed to further delay steroid/antibiotic treatment of the baboons until two hours after all organisms were given (4 hours after E. coli infusion was initiated) and sustained systemic hypotension had occurred making the shock model more clinically relevant to those situations in which the physician is faced with patients with severe hypotension. Results demonstrate the notable effectiveness of MPSS and GS even when they are administered during sustained systemic hypotension: 65% of the baboons survived permanently (7 days or more). However, this survival rate was lower than that obtained when treatment was initiated earlier [1,2]. Surviving animals of the present study developed body surface ulcerations, refused to eat for several days, and lost weight.

After the experiments, we found that two of the treated animals, which died, numbers 4 and 6, had elevated zero time LDH isoenzyme concentrations indicating preexisting lesions of liver or lung. Post mortem examinations confirmed this suspicion. These prior pathophysiological

conditions may have compromised the two animals' ability to recover from shock.

Possible explanations for the success of the steroid/antibiotic combination therapy are suggested by changes in several of the measured parameters of the present study. Treated baboons appeared to have better liver and pancreatic function in that blood glucose and serum insulin concentrations were maintained at higher levels. Renal function was supported as evidenced by urine flow in treated baboons in contrast to the anuria observed in the untreated baboons and significantly smaller elevations of BUN in the treated group. The circulating phagocytic defense system was augmented in the treated baboons as suggested by the appearances of increased mature and immature neutrophil concentrations, and the significantly enhanced killing rates of E. coli. The cardioacceleratory response was depressed in the treated baboons compared with the untreated animals, which is consistent with the alleviation by the steroid of the stress caused by E. coli shock.

Parameters which appeared to be unaltered by steroid/antibiotic treatment were systemic arterial blood pressure, pO_2, pCO_2, pH, base excess, and blood lactate concentrations. Systemic pressure, pCO_2, and base excess were similarly depressed in all animals; pO_2 and pH values remained relatively constant while lactate concentrations were equally elevated in both groups. These parameters were therefore not helpful in predicting probability of survival.

Fluid administration averaged 6 and 7 ml/kg/hr for the 12-hour observation period in untreated and treated baboons, respectively, and hematocrit values remained relatively constant. Results from the present study and our earlier reports in dogs and baboons (1, 2, 5) suggested that fluid administration, neither prevents nor influences survival of animals in E. coli-induced shock.

The explanation for this may be that the volume of blood in the animal's circulation is inappropriately distributed in septic shock as has been suggested in human septic shock patients (7), with blood translocated to the venous segments of the vasculature and other sites (8). So the problem may be more one of inappropriate distribution of blood, rather than a lowered total blood volume. We postulate that this "distributive" defect (7), occurring specifically in septic shock (7), may be prevented or reversed with steroid administration by effecting intravascular shifts of blood from sequestered regions to the active circulation (5, 9).

Our findings have consistently shown that steroid adminstration or antibiotic treatment are separately ineffective in the treatment of E. coli shock in both dogs (5) and primates (1, 3, 4). It appears essential that steroid and antibiotic be given concomitantly. Proposed mechanisms of protection with MPSS and GS infusions against the pathophysiologic effects of E. coli in the baboon have been suggested in a previous report (1) and include improvement of hemodynamic, metabolic, endocrinologic and phagocytic functions resulting in the maintenance of normal morphologic-status of tissues including brain, liver, heart, kidneys, and adrenals (1). Our research has been pursued using the baboon because of the animal's phylogenetic proximity to man as evidenced by increasingly similar findings between the two species (10-13).

REFERENCES

1. Hinshaw, L.B., Archer, L.T., Beller-Todd, B.K., et al. Survival of primates in LD_{100} septic shock following steroid/antibiotic therapy. J Surg Res 1980; 28:151-170.

2. Hinshaw, L.B., Archer, L.T., Beller-Todd, B.K., Benjamin, B., Flournoy, D.J., Passey, R. Survival of primates in lethal septic shock following delayed treatment with steroid. Circ Shock (in press).

3. Hinshaw, L.B., Coalson, J.J., Benjamin, B.A., et al. Escherichia coli shock in the baboon and the response to adrenocorticosteroid treatment. Surg Gynecol Obstet 1978; 147:545-557.

4. Coalson, J.J., Benjamin, B.A., Archer, L.T., Beller, B.K., Spaet, R.H., Hinshaw, L.B. A pathologic study of Escherichia coli shock in the baboon and the response to adrenocorticosteroid treatment. Surg Gynecol Obstet 1978; 147:726-736.

5. Hinshaw, L.B., Beller, B.K., Archer, L.T., Flournoy, D.J., White, G.L., Phillips, R.W. Recovery from lethal Escherichia coli shock in dogs. Surg Gynec Obstet 1979; 149:545-553.

6. Hinshaw, L.B., Benjamin, B., Coalson, J.J., et al. Hypoglycemia in lethal septic shock in subhuman primates. Circ Shock 1975; 2:197-208.

7. Weil, M.H. Proposed reclassification of shock states with special reference to distributive defects. In: Hinshaw, L.B. and Cox, B.G., eds. The Fundamental Mechanisms of Shock. New York: Plenum Press, 1972:13-22.

8. Hinshaw, L.B., Shanbour, L.L., Greenfield, L.J., and Coalson, J.J. Mechanism of decreased venous return in subhuman primate administered endotoxin. Arch Surg 1970; 100:600-606.

9. 'Hinshaw, L.B., Solomon, L.A., Freeny, P.C., and Reins, D.A.
    Endotoxin shock: Hemodynamic and survival effects of methylpred-
    nisolone. Arch Surg 1967; 94:61-66.

10. Schumer, W. Steroids in the treatment of clinical septic shock.
    Ann Surg 1976; 184:333-341.

11. Cerra, F.B., Siegel, J.H., Border, J.R., Wiles, J., and
    McMenamy, R.R. The hepatic failure of sepsis: Cellular versus
    substrate. Surg 1979; 86:409-422.

12. Clowes, G.H.A., Jr., O'Donnell, T.F., Jr., Ryan, N.T., Blackburn, G.L.
    Energy metabolism in sepsis: treatment based on different patterns
    in shock and high output stage. Ann Surg 1974; 179:684-696.

13. Clowes, G.H.A., Martin, H., Walji, S., Hirsch, E., Gazitua, R.,
    Goodfellow, R. Blood insulin responses to blood glucose levels
    in high output sepsis and septic shock. Am J Surg 1978; 135:577-583.

TABLE I

TREATMENT PROTOCOL OF BABOONS FOLLOWING SUSTAINED HYPOTENSION INDUCED BY ESCHERICHIA COLI INFUSION

GROUP	(N)	AGENT ADMINISTERED	DOSAGE	TIME AFTER ON-SET OF E. COLI INFUSION	DURATION AND ROUTE OF ADMINISTRATION
E. coli only	8	E. coli organisms	$2.4(\pm0.2)\times10^{10}$/kg		0-120 min, iv
E. coli + MPSS + GS	8	E. coli organisms	$2.5(\pm0.2)\times10^{10}$/kg		0-120 min, iv
		Methylprednisolone*	30 mg/kg	+ 4 hrs	15 min, iv
		Gentamicin†	9 mg/kg	+ 4 hrs 5 min	60 min, iv
		Methylprednisolone	15 mg/kg	+ 6 hrs	120 min, iv
		Gentamicin	4.5 mg/kg	+ 8 hrs	30 min, iv
		Methylprednisolone	15 mg/kg	+ 9.5 hrs	90 min, iv
		Gentamicin	4.5 mg/kg	+ 11 hrs	30 min, iv
		Methylprednisolone	15 mg/kg	+ 11 hrs	60 min, iv
		Gentamicin	4.5 mg/kg	+ 12 hrs	im
		Gentamicin	4.5 mg/kg	TWICE DAILY, 3 DAYS	im

*methylprednisolone sodium succinate

†gentamicin sulfate

TABLE II

SURVIVAL DATA OF BABOONS ADMINISTERED ESCHERICHIA COLI AND TREATED AFTER

SUSTAINED HYPOTENSION WITH METHYLPREDNISOLONE SODIUM SUCCINATE AND GENTAMICIN SULFATE

Group	Baboon Number	Weight (kg)	E. coli/kg	Sex	Survival Time
E. coli only	1	15.8	2.1×10^{10}	F	11 hrs
	2	16.2	2.1×10^{10}	F	3 hrs
	3	19.9	1.7×10^{10}	M	5 hrs
	4	19.0	2.5×10^{10}	M	32 hrs
	5	18.2	2.3×10^{10}	M	42 hrs
	6	16.0	3.6×10^{10}	M	13 hrs
	7	15.5	2.2×10^{10}	M	16 hrs
	8	14.0	2.7×10^{10}	M	11 hrs
Mean		16.8	2.4×10^{10}		17 hrs
		±	(0.2×10^{10})		
E. coli plus	1	26.6	2.7×10^{10}	M	8 days*
methylprednisolone sodium succinate and gentamicin sulfate	2	15.0	2.1×10^{10}	F	41 hrs
	3	14.4	2.4×10^{10}	F	9 days*
	4	22.7	2.5×10^{10}	M	49 hrs
	5	13.3	3.5×10^{10}	F	15 days*
	6	21.0	2.1×10^{10}	M	10 hrs
	7	14.9	2.4×10^{10}	M	14 days*
	8	15.7	2.5×10^{10}	M	7 days*
Mean		17.9	2.5×10^{10}		
		±	(0.2×10^{10})		

*euthanized

TABLE III

ESCHERICHIA COLI COLONY FORMING UNITS PER ML BLOOD IN BABOONS ADMINISTERED LD$_{100}$ ESCHERICHIA COLI

AND TREATED AFTER SUSTAINED HYPOTENSION WITH METHYLPREDNISOLONE SODIUM SUCCINATE AND GENTAMICIN SULFATE

Group		No. E. coli infused per kg body weight	Zero time	+125 min	+4 hr	+6 hr	+12 hr
E. coli only	Mean	2.4×10^{10}	Negative	1.5×10^{7}	2.5×10^{3}	1.1×10^{3}	1.2×10^{3}
	SE ($\pm$)	0.2×10^{10}		0.8×10^{7}	0.9×10^{3}	0.4×10^{3}	0.5×10^{3}
	N	8	8	8	7	6	4
E. coli plus *MPSS and *GS	Mean	2.5×10^{10}	Negative	1.0×10^{7}	1.5×10^{4}	1.1×10^{2}	1.6×10^{2}
	SE ($\pm$)	0.2×10^{10}		0.3×10^{7}	0.8×10^{4}	0.3×10^{2}	0.8×10^{2}
	N	8	8	8	8	8	7
	P					< 0.02	< 0.02

*MPSS = methylprednisolone sodium succinate
*GS = gentamicin sulfate

LEGENDS FOR ILLUSTRATIONS

Figure 1. Changes in mean systemic arterial pressure and heart
rate (M±SE) in baboons receiving E. coli alone, and those with E. coli
followed by intermittent infusions of methylprednisolone sodium
succinate (MPSS) and gentamicin sulfate (GS). MPSS and GS infusions
were begun 4 hours after the onset of a two-hour infusion of LD_{100}
E. coli (N=8, each group).

□,☆ = p < 0.05, paired comparisons within each group with zero time value.

△ = p < 0.05, unpaired comparison between groups.

Figure 2. Alterations in blood glucose and serum insulin concen-
trations in treated and untreated baboons receiving LD_{100} infusions of
E. coli (M±SE) (N=8, each group). Methylprednisolone sodium succinate
(MPSS) and gentamicin sulfate (GS) infusions were begun 4 hours after
the onset of a two-hour infusion of E. coli.

□,☆ = p < 0.05, paired comparisons within each group with zero time values.

= p < 0.05, unpaired comparison between groups.

Figure 3. Changes in concentrations of mature and immature neutro-
phils, lymphocytes and platelets in baboons receiving E. coli alone
versus those receiving E. coli and subsequently treated with methylpred-
nisolone sodium succinate (MPSS) and gentamicin sulfate (GS). (N=8, each
group, M±SE).

□,☆ = p < 0.05, paired comparisons within each group with zero time values.

△ = p < 0.05, unpaired comparison between groups.

Figure 4. Alterations in respiratory, acid-base parameters and
lactate concentrations in baboons receiving E. coli alone and E. coli
plus subsequent infusions of methylprednisolone sodium succinate (MPSS)
and gentamicin sulfate (GS). (N=8, each group, M±SE).

□,☆ = p < 0.05, paired comparisons within each group with zero time values.

Figure 5. Changes in blood urea nitrogen and creatinine concentrations in treated and untreated baboons   (N=8, each group, M±SE).

Lower portion of figure = serum gentamicin sulfate concentrations in treated group.

□,☆ = $p < 0.05$, paired comparisons within each group with zero time values.
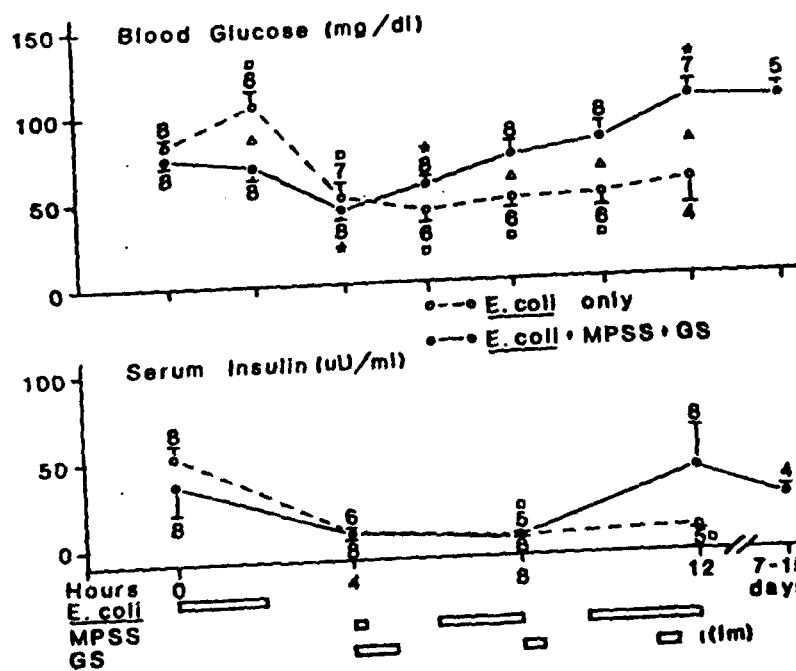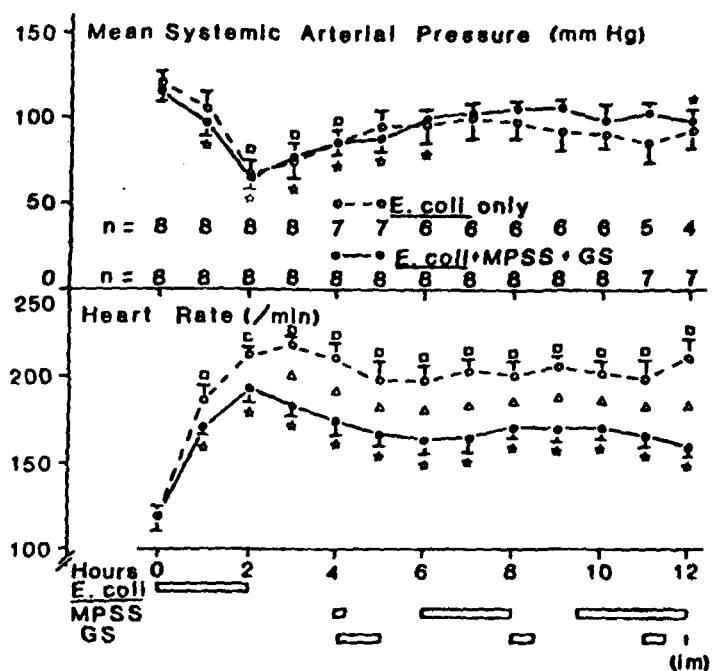
Δ = $p < 0.05$, unpaired comparison between groups.

FIGURE 1

FIGURE 2

FIGURE 3

FIGURE 4

Blood Urea Nitrogen (mg/dl)

60

40

20

0

•--• E. coli only
•—• E. coli + MPSS + GS

Serum Creatinine (mg/dl)

5

2.5

0

Hours	0	4	8	12	7-15 days

E. coli

MPSS

GS

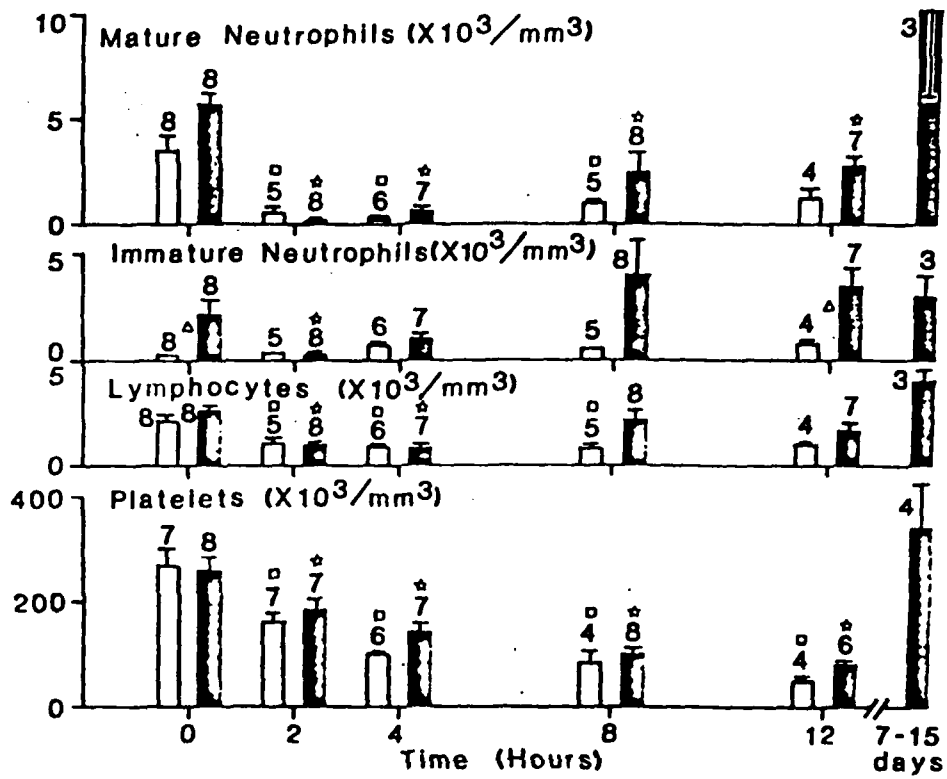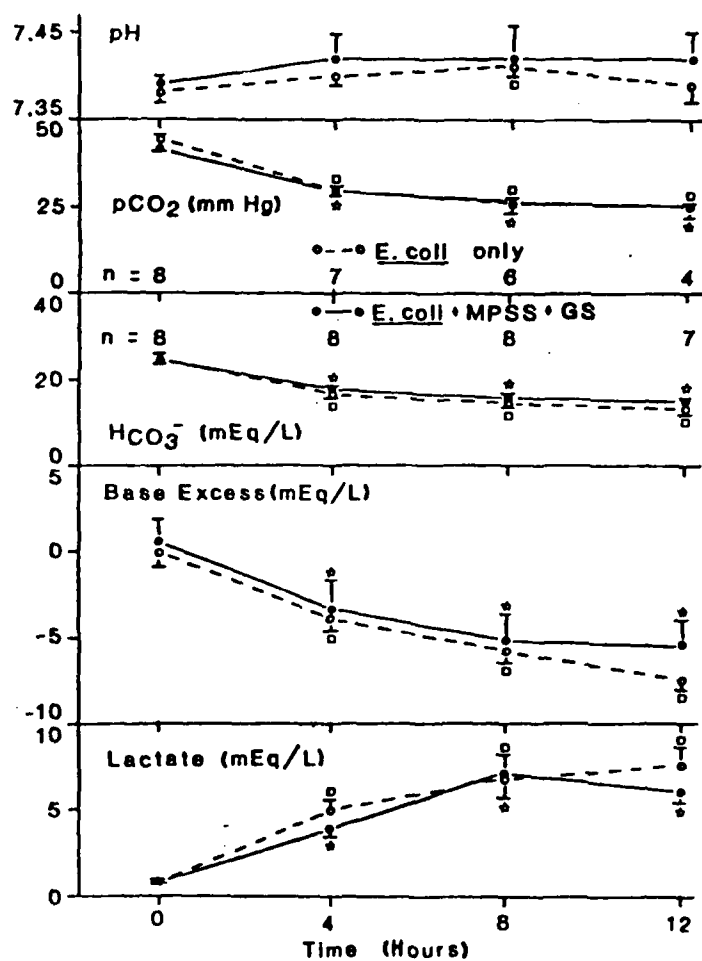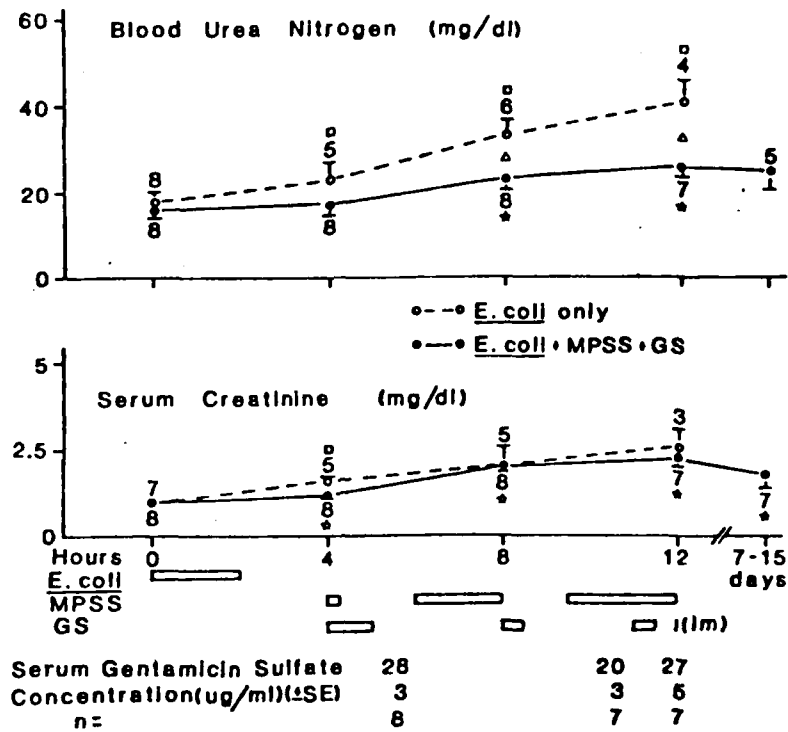| Serum Gentamicin Sulfate	28		20	27
Concentration(ug/ml)(±SE)	3		3	5
n=	8		7	7

FIGURE 5

OFFICE OF NAVAL RESEARCH
BIOLOGICAL SCIENCES DIVISION
BIOPHYSICS PROGRAM, Code 444
DISTRIBUTION LIST FOR TECHNICAL, ANNUAL AND FINAL REPORTS

Number of Copies

(13)	Administrator, Defense Documentation Center Cameron Station Alexandria, Virginia 22314
(6)	Director, Naval Research Laboratory Attention: Technical Information Division Code 2627 Washington, D. C. 20375
(6)	Office of Naval Research Attention: Code 102IP (ONRL DOC) 800 N. Quincy Street Arlington, Virginia 22217
(3)	Office of Naval Research Biophysics Program Code 444 Arlington, Virginia 22217
(1)	Commanding Officer Naval Medical Research and Development Command National Naval Medical Center Bethesda, Maryland 20014
(1)	Chief, Bureau of Medicine and Surgery Department of the Navy Washington, D. C. 20375
(2)	Technical Reference Library Naval Medical Research Institute National Naval Medical Center Bethesda, Maryland 20014
(1)	Office of Naval Research Branch Office Building 114, Section D 666 Summer Street Boston, Massachusetts 02210
(1)	Office of Naval Research Branch Office 536 South Clark Street Chicago, Illinois 60605

(1)   Office of Naval Research Branch Office
1030 East Green Street
Pasadena, California   91106

(1)   Commanding Officer
Naval Medical Research Unit No. 2
Box 14
APO San Francisco   96263

(1)   Commanding Officer
Naval Medical Research Unit No. 3
FPO New York   09527

(1)   Officer in Charge
Submarine Medical Research Laboratory
Naval Submarine Base, New London
Groton, Connecticut   06342

(1)   Scientific Library
Naval Aerospace Medical Research Institute
Naval Aerospace Medical Center
Pensacola, Florida   32512

(1)   Commanding Officer
Naval Air Development Center
Attn: Aerospace Medical Research Department
Warminster, Pennsylvania   18974

(1)   DIRECTOR
Naval Biosciences Laboratory
Building 844
Naval Supply Center
Oakland, California   94625

(1)   Commander, Army Research Office
P. O. Box 12211
Research Triangle Park
North Carolina   27709

(1)   DIRECTORATE OF LIFE SCIENCES
Air Force Office of Scientific Research
Bolling Air Force Base
Washington, D. C.   20332

(1)   Commanding General
Army Medical Research and Development Command
Forrestal Building
Washington, D. C.   20314

(1)   Department of the Army
                          U. S. Army Science and
                            Technology Center - Far East
                          APO San Francisco   96328

(1)   Assistant Chief for Technology
                          Office of Naval Research, Code 200
                          800 N. Quincy Street
                          Arlington, Virginia   22217